Complete Summary

GUIDELINE TITLE

Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Methylphenidate atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Mar. 34 p. (Technology appraisal; no. 98).

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references drugs for which important revised regulatory information has been released.

- August 21, 2006, Dexedrine (dextroamphetamine sulfate): Changes to the BOXED WARNING, WARNINGS and PRECAUTIONS sections of the prescribing information.
- September 29, 2005, Strattera (atomoxetine): Manufacturer asked to revise the prescribing information to include a boxed warning and additional warning statements that alert health care providers of an increased risk of suicidal thinking in children and adolescents.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Attention deficit hyperactivity disorder (ADHD)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Pediatrics
Psychiatry

INTENDED USERS

Advanced Practice Nurses
Patients
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To examine the clinical and cost-effectiveness of oral methylphenidate hydrochloride, dexamfetamine sulphate and atomoxetine in children and adolescents (under 18 years of age) diagnosed with attention deficit hyperactivity disorder (ADHD) (including hyperkinetic disorder)

TARGET POPULATION

Children and adolescents (under 18 years of age) diagnosed with attention deficit hyperactivity disorder (ADHD) (including hyperkinetic disorder)

INTERVENTIONS AND PRACTICES CONSIDERED

1. Methylphenidate hydrochloride
2. Atomoxetine sulphate
3. Dexamfetamine

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness
    - Quality of life
    - Symptom improvement
    - Adverse effects of pharmacological agents
- Cost-effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Centre for Reviews and Dissemination, University of York. (See the "Companion Documents" field.)

Search Strategy

The search strategies aimed to retrieve papers relating to methylphenidate, dexamfetamine, and atomoxetine for children with attention deficit hyperactivity disorder (ADHD). The strategy was based on that used in the Agency for Healthcare Research and Quality (AHRQ) report. A date restriction of 1999 onwards was placed on the methylphenidate searches as this review updates the report produced by Paisley and Lord published in 2000. A date restriction of 1997 onwards was placed on the searches for dexamfetamine in order to update the AHRQ report. Research on atomoxetine was searched for from 1981 onwards.

Inclusion/Exclusion Criteria

Two reviewers independently screened all titles and abstracts including economic evaluations. Full paper manuscripts of any titles/abstracts that were considered relevant by either reviewer were obtained and assessed for inclusion or exclusion. Any discrepancies were resolved by consensus and if necessary, a third reviewer was consulted. In addition, full paper copies of relevant studies presented in the NICE, AHRQ and Canadian Coordinating Office of Health Technology and Assessment (CCOHTA) reports were obtained. For the assessment of clinical effectiveness, randomised controlled trials (RCTs) examining methylphenidate, dexamfetamine or atomoxetine used alone, in combination with each other, or in combination with non-drug interventions that were compared to placebo, to one another in head-to-head comparisons, or compared to non-drug interventions were included in the review. This was applied to both efficacy and adverse events data. In addition, systematic reviews (SRs) were included to examine adverse events data. For the assessment of cost-effectiveness, a broader range of studies was considered. Participants included children and adolescents less than 18 years of age diagnosed with ADHD (including hyperkinetic disorder). There was no lower age limitation.

Note: For detailed information on literature search strategies, see the Assessment Report prepared by the Centre for Reviews and Dissemination, University of York. (See the "Companion Documents" field.)

NUMBER OF SOURCE DOCUMENTS

In the previous systematic reviews (National Institute for Health and Clinical Excellence [NICE], Agency for Healthcare Research and Quality [AHRQ], and Canadian Coordinating Office of Health Technology and Assessment [CCOHTA]), 65 studies were identified that may be relevant to the current systematic review, and full paper copies were ordered. Of these, 40 met the inclusion criteria.

A total of 2908 titles and abstracts relating to clinical effectiveness or systematic reviews of adverse events were identified and screened for relevance -- some of which were obtained by checking references of relevant studies.

Of these, 409 full paper copies were examined in detail and assessed for inclusion. Of these 20 randomised controlled trials (RCTs) and 1 systematic review (SR) met the inclusion criteria. In addition, four commercial-in-confidence (CIC) papers were included. Overall, this gives a total of 65 papers (40 papers from previous systematic reviews, 21 papers from the updated search and 4 CIC papers). An additional 53 papers/abstracts related to the trials presented in the 65 papers. These were not considered to be fully included, but are referenced in the data extraction tables with the studies that they relate to. Reasons for exclusions are presented for each of the 117 papers from the updated search in Appendix 3 and for each of the 25 papers from the previous reviews in Appendix 4 of the Assessment Report (see the "Companion Documents" field).

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Centre for Reviews and Dissemination, University of York. (See the "Companion Documents" field.)

Data Extraction and Quality Assessment

Data relating to both study design and quality were extracted by one reviewer and independently checked for accuracy by a second reviewer. Any discrepancies were resolved by consensus and if necessary, a third reviewer was consulted. Data from studies with multiple publications were extracted and reported as a single study.

Methods of Analysis/Synthesis

Clinical effectiveness data were reported separately for each drug -- and by the type of comparison. Data for methylphenidate hydrochloride was also analysed separately based on whether it was administered as an immediate release or extended release formulation. For all drugs, the data was examined by dose. Data for the core outcomes of hyperactivity (using any scale), Clinical Global Impression (as a proxy of quality of life) and adverse events were reported. For cross-over studies, the mean and standard deviation (SD) for each outcome was data extracted for end of trial data (i.e., baseline data was not considered). Where possible, we aimed to calculate mean difference and standard errors for cross-over studies in order to facilitate metaanalysis. However, due to the lack of information needed to calculate mean differences in many of the studies, this was not possible. For parallel studies, change scores were reported where given, otherwise means and SDs were presented for end of trial data. In addition, mean differences with 95% confidence intervals (CIs) were calculated for each study. For adverse events, the review focused on four key events: loss of appetite, insomnia, headache and stomach-ache. For the cost-effectiveness section of the report, details of each identified published economic evaluation, together with a critical appraisal of its quality, were presented in structured tables.

Handling Company Submissions

All the clinical effectiveness data included in the company submissions were assessed. Where this met the inclusion criteria it was included in the clinical effectiveness review. All economic evaluations (including accompanying models) included in the company submissions were assessed and detailed assessments of the assumptions underlying the submitted analyses were undertaken. A new model was developed to assess the cost-effectiveness of the alternative treatments in terms of cost per quality-adjusted life-year (QALY). To achieve this a mixed treatment comparison (MTC) model was used to estimate the differential mean response rates. Monte-Carlo simulation was used to reflect uncertainty in the cost-effectiveness results.

Note: For detailed information on the methods used to analyze the evidence, see the Assessment Report prepared by the Centre for Reviews and Dissemination, University of York. (See the "Companion Documents" field.)

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Cost Effectiveness

Seven published studies were found; five of these were economic evaluations and two were quality of life studies. The Assessment Group developed a model to compare the cost effectiveness of different drug strategies. Three consultees included economic evaluations in their submissions.

To summarise, the results of the published economic evaluations are difficult to compare. All studies suffer from a lack of data, and none consider the long-term outcomes or adverse events associated with attention deficit hyperactivity disorder (ADHD). The results of the Assessment Group model suggest that methylphenidate, dexamfetamine and atomoxetine are all cost-effective treatments for ADHD. However, given the limited data used to inform response and withdrawal rates and the small differences in benefits between different treatments, it is not possible to compare different drug strategies. All three manufacturers adopted different approaches to the estimation of treatment effectiveness and associated utility values. However, the models all generated incremental cost-effectiveness ratios falling below £20,000 per quality-adjusted life year gained.

Note: See Section 4.2 of the original guideline document for a detailed discussion of the cost-effectiveness analysis.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

1. Where drug treatment is considered appropriate, methylphenidate, atomoxetine and dexamfetamine are recommended, within their licensed indications, as options for the management of attention deficit hyperactivity disorder (ADHD) in children and adolescents.
2. The decision regarding which product to use should be based on the following:
    - the presence of comorbid conditions (for example, tic disorders, Tourette's syndrome, epilepsy)
    - the different adverse effects of the drugs
    - specific issues regarding compliance identified for the individual child or adolescent, for example problems created by the need to administer a mid-day treatment dose at school
    - the potential for drug diversion (where the medication is forwarded on to others for non-prescription uses) and/or misuse
    - the preferences of the child/adolescent and/or his or her parent or guardian.
3. If there is a choice of more than one appropriate drug, the product with the lowest cost (taking into account the cost per dose and number of daily doses) should be prescribed.
4. Drug treatment should only be initiated by an appropriately qualified healthcare professional with expertise in ADHD and should be based on a comprehensive assessment and diagnosis. Continued prescribing and monitoring of drug therapy may be performed by general practitioners, under shared care arrangements.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents

POTENTIAL HARMS

Methylphenidate

Common adverse effects of treatment include insomnia, nervousness, headache, decreased appetite, abdominal pain and other gastrointestinal symptoms, and cardiovascular effects such as tachycardia, palpitations and minor increases in blood pressure.

Dexamfetamine

Common adverse effects are similar to those of methylphenidate.

Atomoxetine

Common adverse effects of treatment include abdominal pain, decreased appetite, nausea and vomiting, early morning awakening, irritability and mood swings. Increased heart rate and small increases in blood pressure were observed in clinical trials.

Note: For full details of adverse effects and contraindications, see the relevant Summary of Product Characteristics.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation and Audit

- National Health Service (NHS) organisations that offer treatment for children and adolescents with attention deficit hyperactivity disorder (ADHD) and general practitioners (GPs) should review their current practice and policies to take account of the guidance (see the "Major Recommendations" field).
- Local guidelines, protocols or care pathways that refer to the care of children and adolescents with ADHD should incorporate the guidance.
- To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C of the original guideline document.
    - Drug treatment for a child or adolescent with ADHD is initiated only by an appropriately qualified healthcare professional with expertise in ADHD, and is based on a comprehensive assessment and diagnosis.

        - Where drug treatment is considered appropriate, methylphenidate, atomoxetine or dexamfetamine is offered, within licensed indications, as an option in the management of ADHD in a child or adolescent.
        - The decision regarding which product to use considers the following:
            - the presence of comorbid conditions
            - the different adverse effects of the drugs
            - specific issues regarding compliance identified for the individual child or adolescent
            - the potential for drug diversion and/or misuse
            - the preferences of the child or adolescent and/or his or her parent or guardian
        - If there is a choice of more than one appropriate drug, the drug with the lowest cost is prescribed.
    - Local clinical audits on the management of ADHD in children or adolescents could also include the following: ensuring that children or adolescents and their parents are informed about ADHD, treatment options, and the importance of medication compliance; clinician follow-up on any effects of drug treatment; compliance with national or local guidelines on the management of ADHD or shared care arrangements with local general practitioners; and planning for the continuation of care for adolescents who are approaching the age for moving from child and adolescent care services to adult services.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Patient Resources
Quick Reference Guides/Physician Guides

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Methylphenidate atomoxetine and dexamfetamine for attention deficit hyperactivity disorder

(ADHD) in children and adolescents. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Mar. 34 p. (Technology appraisal; no. 98).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Mar

GUIDELINE DEVELOPER(S)

National Institute for Health and Clinical Excellence - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Appraisal Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Committee Members: Dr Jane Adam, Radiologist, St George's Hospital, London; Professor Ron Akehurst, Dean of School of Health and Related Research, University of Sheffield; Dr Sunil Angris, General Practitioner, Waterhouses Medical Practice, Staffordshire; Professor David Barnett (Chair) Professor of Clinical Pharmacology, University of Leicester; Professor Stirling Bryan, Professor of Health Economics, Health Economics Facility, Health Services Management Centre, University of Birmingham; Professor John Cairns, Professor of Health Economics, Public Health and Policy, London School of Hygiene and Tropical Medicine; Professor David Chadwick, Professor of Neurology, Department of Neurological Science, Walton Centre for Neurology & Neurosurgery, Liverpool; Dr Lorna Duggan, Consultant Forensic Psychiatrist in Developmental Disabilities, St Andrew's Hospital, Northampton; Mrs Fiona Duncan, Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool; Dr Paul Ewings, Statistician, Taunton & Somerset NHS Trust, Taunton; Dr Trevor Gibbs, Head, Global Clinical Safety & Pharmacovigilance, GlaxoSmithKline, Greenford; Professor Philip Home (Vice-Chair) Professor of Diabetes Medicine, Department of Medicine, University of Newcastle upon Tyne; Dr Peter Jackson, Clinical Pharmacologist, Molecular & Clinical Pharmacology, University of Sheffield; Dr Mike Laker, Medical Director, Newcastle Hospitals NHS Trust, Royal Victoria Infirmary, Newcastle-Upon-Tyne; Dr George Levvy, Chief Executive, Motor Neurone Disease Association, Northampton; Mr Terence Lewis, Mental Health Consultant, National Institute for Mental Health in England, Solihull, West Midlands; Professor Richard Lilford, Professor of Clinical Epidemiology, Department of Public Health and Epidemiology, University of Birmingham; Professor John Lumley, Honorary Consultant, The Ernest Cooke Clinic Microvascular Unit, Great Ormond Street,

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Mar. 2 p. (Technology appraisal 98). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- Methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children. Assessment report. Centre for Reviews and Dissemination, Centre for Health Economics, University of York; 2004 Dec 9. 606 p. Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N1010. 11 Strand, London, WC2N 5HR.

PATIENT RESOURCES

The following is available:

- Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents. Understanding NICE guidance - information for children and adolescents with ADHD, their families and carers, and the public. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Mar. 7 p. (Technology appraisal 98).

Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site

Print copies: Available from the Department of Health Publications Order Line 0870 1555 455. ref: N1011. 11 Strand, London, WC2N 5HR.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This NGC summary was completed by ECRI on May 19, 2006. This summary was updated by ECRI on September 7, 2006 following the updated U.S. Food and Drug Administration advisory on Dexedrine.

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